CURRENT LITERATURE

ANTIEPILEPTIC DRUGS AND HOMOCYSTEINE LEVELS

Antiepileptic Drugs as Independent Predictors of Plasma Total Homocysteine Levels

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Low folate levels have consistently been reported in patients with epilepsy on phenytoin (PHT), phenobarbital (PB) and primidone (PRD), while data on valproate (VPA) are conflicting. Furthermore, antiepileptic drugs (AEDs) may be associated with high levels of plasma total homocysteine (p-tHcy). Therefore, we have investigated the levels of p-tHcy, serum folate (S-FA) and erythrocyte folate (E-FA) in patients on PHT, PB and PRD (Group 1, n=21) and VPA (Group 2, n=24). Both groups had their own matched controls. Blood samples were drawn fasting and 6 h post methionine loading (6 h-PML). The Group 1 patients had fasting and 6 h-PML p-tHcy levels significantly higher than their controls (P=0.05 and <0.0001, respectively), and patients without dietary multivitamin supplementation (n=14), had lower fasting S-FA and E-FA levels than their controls (P=0.02 and 0.0003, respectively). The Group 2 patients had fasting and 6 h-PML levels of p-tHcy, S-FA and E-FA not different from their controls. In a multiple stepwise regression model comprising all subjects (n=90), the AEDs of Group 1 and the S-FA levels were independent predictors of p-tHcy levels. Thus, PHT, PB and PRD are associated with high p-tHcy and low folate levels, whereas VPA does not influence S-FA, E-FA and p-tHcy levels in adult patients.

COMMENTARY

In 1997, Ono et al. (1) reported on the risk of high total plasma homocysteine levels (p-Hcy) in patients taking enzyme-inducing antiepileptic drugs (EIAEDs); this study suffered from a lack of stringent controls, however. Two years later, Schwaninger et al. published a well-controlled study that demonstrated that EIAEDs could indeed cause significant elevations of p-Hcy (2). These authors attributed it to low folic acid levels, as they found an inverse correlation between the

two. In this article, Apeland et al. confirmed these observations but demonstrated that EIAEDs are, by themselves, independent predictors of a high p-Hcy level. In addition, these authors demonstrated that the measurement of the p-Hcy level at 6 hours after a postmethionine load (PML) yields a higher sensitivity to detect hyperhomocysteinemia.

Clinicians, however, have paid relatively little attention to this potentially serious adverse event of EIAEDs. Indeed, epidemiologic studies have clearly established a significantly higher risk of coronary artery disease, cerebrovascular disease, peripheral vascular disease, and venous thrombosis with p-Hcy levels >15 to 20 μ mol/L. Approximately 10% of CVA has been attributed to high p-Hcy levels (3–5). Cerebrovascular disease presents primarily as small vessel vascular disease and appears to facilitate the development of multi-infarct dementia (6). In addition, three recent case-control studies have found an association between a high p-Hcy level and dementia of the Alzheimer's type (7–9). A high p-Hcy level has been also associated with an increased risk of neural tube defects (10). Finally, a high p-Hcy level (50 to 200 μ mol/L) can be associated with an increased risk of seizures (11).

Clearly, the potential comorbidity associated with a high p-Hcy level is significant. After all, EIAEDs such as phenytoin and carbamazepine are still among the most widely prescribed AEDs in patients with seizures following a CVA and in the older population, the age group in which the p-Hcy levels increase more than in other age groups (6). In so doing, are we increasing the risk of recurrent small vessel stroke or an acceleration of a multi-infarct dementia? This question has yet to be answered. There are some data, however, that may support this concern: Annegers et al., for example, demonstrated that younger adults (aged 25 to 64 years) with epilepsy and cerebrovascular disease had an increased mortality that was related to ischemic heart disease (12). In this study, the presence of an AED had no impact on the ischemic heart disease, but the data analysis did not break down the AEDs by type.

The data from this study demand that we consider the following precautions when prescribing EIAEDs: (a) identifying patients with a genetic risk of hyperhomocysteinemia, such as the patients homozygous for the C677T mutation, which comprise 5% to 10% of the general population (13); (b) measuring fasting and PML p-Hcy in patients treated with EIAEDs, and particularly those at greater risks of homocysteinemia, such

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as the older population; (c) measuring the fasting and PML p-Hcy level in women planning to get pregnant who are on EIAEDs; (d) considering the use of new AEDs (that do not induce hepatic enzymes) in patients at risk of hyperhomocysteinemia or the prescription of combination therapy with folic acid \pm vitamin $B_6 \pm B_{12}$, as it has been shown to reverse it (6). However, whether vitamin therapy has the same impact in AED-induced homocysteinemia is yet to be established.

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